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~~76~~. (Amended) An isolated *Hepadnavirus* mutant, comprising a mutation in the gene encoding the DNA polymerase, resulting in decreased sensitivity to a nucleoside analogue compared to a wild-type *Hepadnavirus*, wherein said mutation results in at least one amino acid addition, substitution, and/or deletion in the B domain corresponding to amino acid residues 505-529 of a wild-type HBV polymerase, and said mutant contains an unmutated YMDD motif in the C domain.

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Add the following claim.

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~~80~~. (New) A method for determining the potential for an HBV to exhibit, relative to an isolated wild-type HBV, reduced sensitivity to an anti-viral agent, said method comprising isolating DNA or corresponding mRNA from said HBV and screening for a mutation in a nucleotide sequence encoding the B domain of HBV polymerase corresponding to amino acid residues 495-535 of a wild-type HBV polymerase, with said mutation resulting in at least one amino acid substitution, deletion and/or addition in said B domain,

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wherein the presence of such a mutation is an indication of the potential of reduced sensitivity of said HBV to an anti-viral agent.--

REMARKS

Reconsideration is requested.

The telephonic interview with the Examiner on August 13, 2002, is acknowledged, with appreciation. The claims have been amended above with the understanding that the Amendment Under Rule 116 filed June 17, 2002, has been entered. The claims have been amended as discussed with the Examiner, to advance prosecution, without prejudice, to specify, as one disclosed embodiment of the present specification, mutants wherein the YMDD motif of the C domain is unmutated. The

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allowance of claims 58 and 65-72, and indication that claims 78 and 79 contain allowable subject matter, in the Advisory Action dated July 10, 2002, is acknowledged, with appreciation. Claims 61 and 62 have been amended to be supported by the claims from which they depend. Claims 73 has been canceled, without prejudice, to advance prosecution. Claim 80 has been added and is similar to allowed claim 65 but for the recitation of "an anti-viral agent" in place of the specific agents recited in allowed claim 65. Support for the recitation may be found, for example, on page 2, lines 8-11 of the specification.

Claims 55-79 are pending. Claims 55-72 and 74-79 will be pending upon entry of the present Amendment.

The applicants believe the specification describes the subject matter of the amended claims in that mutants are described which may contain mutations in the B and/or C domains of DNA polymerase. See, for example, pages 4 and 5 of the specification. The description of optional alternative mutations is believed to describe mutations in B domain and not in the C domains as well as the C domain and not in the B domain. Moreover, the examples describe patient samples wherein B domain mutations were found without mutations in the YMDD motif of the C domain. Accordingly, the subject matter of the amended claims is believed to be described in the present specification.

The amended claims are submitted to be patentable over the art of record.

Entry of the above and allowance of the pending claims are requested.

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The Examiner is requested to contact the undersigned in the event anything further is required.

Respectfully submitted,

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MARKED-UP COPY OF AMENDED CLAIMS

IN THE CLAIMS

Amend the claims as follows:

Cancel claim 73, without prejudice.

55. (Amended) An isolated HBV mutant, comprising a mutation in the gene encoding the HBV DNA polymerase resulting in decreased sensitivity to a nucleoside analogue compared to a wild-type HBV, wherein said mutation results in at least one amino acid addition, substitution, and/or deletion in the B domain corresponding to amino acid residues 495-535 of a wild-type HBV polymerase, and said mutant contains an unmutated YMDD motif in the C domain.

56. (Amended) An isolated HBV mutant, comprising a mutation in the gene encoding the HBV DNA polymerase resulting in decreased sensitivity to a nucleoside analogue compared to a wild-type HBV, wherein said mutation results in at least one amino acid addition, substitution, and/or deletion in the B domain corresponding to amino acid residues 505-535 of a wild-type HBV polymerase, and said mutant contains an unmutated YMDD motif in the C domain.

57. (Amended) An isolated HBV mutant, comprising a mutation in the gene encoding the HBV DNA polymerase resulting in decreased sensitivity to a nucleoside analogue compared to a wild-type HBV, wherein said mutation results in at least one amino acid addition, substitution, and/or deletion in the B domain corresponding to amino acid residues 505-529 of a wild-type HBV polymerase, and said mutant contains an unmutated YMDD motif in the C domain.

60. (Amended) The HBV mutant according to any of claims 55 or 58 wherein said [at least one amino acid substitution] mutation is selected from the group consisting

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of Arg/Trp499Glu, Phe512Leu, Val519Leu, Pro523Leu, Leu526Met, Thr530Ser, and Ile533Leu.

61. (Amended) The HBV mutant according to claim 59 wherein said [at least one amino acid substitution] mutation is selected from the group consisting of Arg/Trp499Glu, Phe512Leu, Val519Leu, Pro523Leu, Leu526Met, Thr530Ser, and Ile533Leu.

62. (Amended) An isolated HBV mutant exhibiting, relative to an isolated wild-type HBV, reduced sensitivity to a nucleoside analogue, said mutant comprising at least one mutation in its genome wherein said at least one mutation produces at least one amino acid substitution in the DNA polymerase selected from the group consisting of Trp/Arg499Glu, Phe512Leu and Val519Leu, said amino acid substitution in the DNA polymerase resulting in a concurrent amino acid substitution in the overlapping open reading frame of the HBV surface antigen, and said mutant contains an unmutated YMDD motif in the C domain.

63. (Amended) An isolated HBV mutant exhibiting, relative to an isolated wild-type HBV, reduced sensitivity to a nucleoside analogue, said mutant comprising at least one mutation in its genome wherein said at least one mutation produces at least one amino acid substitution in the DNA polymerase selected from the group consisting of Trp/Arg499Glu, Phe512Leu, Val519Leu and Ser559Thr, said amino acid substitution in the DNA polymerase resulting in a concurrent amino acid substitution in the overlapping open reading frame of the HBV surface antigen, and said mutant contains an unmutated YMDD motif in the C domain.

74. (Amended) An isolated *Hepadnavirus* mutant, comprising a mutation in the gene encoding the DNA polymerase, resulting in decreased sensitivity to a nucleoside

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analogue compared to a wild-type *Hepadnavirus*, wherein said mutation results in at least one amino acid addition, substitution, and/or deletion in the B domain corresponding to amino acid residues 495-535 of a wild-type HBV polymerase, and said mutant contains an unmutated YMDD motif in the C domain.

75. (Amended) An isolated *Hepadnavirus* mutant, comprising a mutation in the gene encoding the DNA polymerase, resulting in decreased sensitivity to a nucleoside analogue compared to a wild-type *Hepadnavirus*, wherein said mutation results in at least one amino acid addition, substitution, and/or deletion in the B domain corresponding to amino acid residues 505-535 of a wild-type HBV polymerase, and said mutant contains an unmutated YMDD motif in the C domain.

76. (Amended) An isolated *Hepadnavirus* mutant, comprising a mutation in the gene encoding the DNA polymerase, resulting in decreased sensitivity to a nucleoside analogue compared to a wild-type *Hepadnavirus*, wherein said mutation results in at least one amino acid addition, substitution, and/or deletion in the B domain corresponding to amino acid residues 505-529 of a wild-type HBV polymerase, and said mutant contains an unmutated YMDD motif in the C domain.